

EXHIBIT F



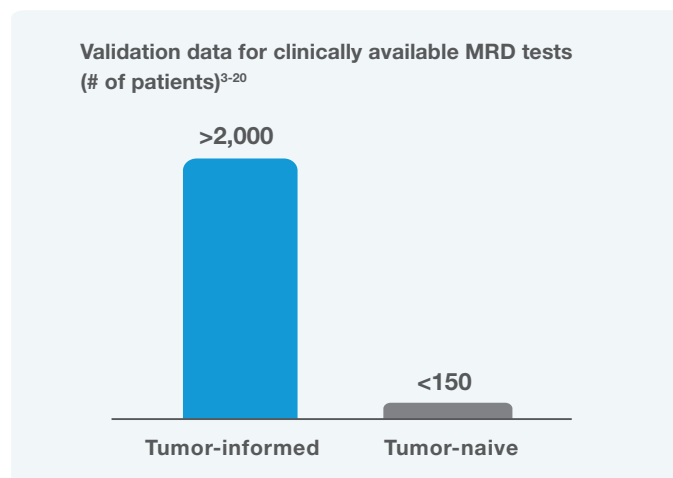
Signatera™
Residual disease test (MRD)

A comparison of tumor-informed and tumor-naïve approaches for early-stage molecular residual disease (MRD) detection

Introduction

Circulating tumor DNA (ctDNA) has emerged as a dynamic biomarker for the assessment of MRD and risk of recurrence in real time.¹ A ctDNA assay optimized for MRD detection must be able to detect ctDNA at the lowest level of residual disease burden, the point at which patients are most likely to benefit from therapeutic intervention.² Currently there are two approaches for assessing MRD using ctDNA: one that is informed by genomic sequencing of the primary tumor (tumor-informed), and another that is uninformed by the mutations in the primary tumor (tumor-naïve). Below, we present the current body of evidence comparing tumor-informed and tumor-naïve approaches, concluding that the tumor-informed approach has stronger validation and better test performance at landmark time points after definitive treatment, as well as in longitudinal monitoring for recurrence and therapeutic response (Figure 1).³⁻²⁰

Figure 1. Body of clinical validation data for commercially available MRD tests



The personalized design of Signatera offers several benefits over tumor-naïve tests:

1. Enhanced limit of detection:

By identifying and tracking clonal variants, which are expected to be present in every cancer cell from the patient, the Signatera approach ensures that residual disease can be detected with both a high sensitivity and high specificity. Signatera can reliably detect tumor-specific variants at a variant allele frequency (VAF) of 0.01%, while tumor-naïve tests are less sensitive, with reliable detection limited to 0.1%–1% VAF.^{3-6,21-26}

2. Filtering of CHIP and germline variants:

Signatera significantly reduces the false-positive rates by filtering out clonal hematopoiesis of indeterminate potential (CHIP) and germline-derived variants from analysis. CHIP and germline variants are well-established sources of biological noise and are a common cause of false-positives in cell free DNA (cfDNA) analysis.²⁷ By sequencing matched peripheral blood samples to the same depth as the biopsied tumor tissue during assay design, Signatera increases the likelihood of tracking true tumor-derived clonal variants.

Two different approaches: to personalize or not to personalize

Tumor-informed strategy

Tumor-informed ctDNA assays leverage the mutational signature derived from the primary tumor to create a customized assay specifically intended for longitudinal ctDNA assessment in patients. The Signatera approach starts with whole-exome sequencing of ~20,000 genes from both the primary tumor and the matched normal tissue (peripheral blood mononuclear cells [PBMCs]). A set of clonal, somatic, single-nucleotide variants, unique to each patient's tumor, is identified to custom design a multiplex PCR (mPCR) assay. The personalized, Signatera mPCR assay can then be used to detect the presence and quantity of ctDNA in the patient's blood with next-generation sequencing. The time it takes to design the custom Signatera assay is two to three weeks, which includes whole-exome sequencing and primer design. After the initial assay is designed, the results for subsequent Signatera assays are reported in five to seven days.

Tumor-naive strategy

Tumor-naive assays are designed to detect ctDNA using a static, preselected panel of actionable or hotspot tumor mutations in advanced cancers. Because of the inherent limitations of the fixed gene panel approach, which impacts sensitivity and specificity, tumor-naive assays are sometimes supplemented with epigenomics (i.e., methylation and fragmentomics) to detect MRD. However, evaluating epigenomics is associated with disadvantages such as lack of quantitation, susceptibility to false positives, and unknown sensitivity. Only limited analytical and clinical data have been publicly disclosed to date.^{19, 20}

- **Sensitivity is impacted by limited number of variants to track.**
The inherent heterogeneity of tumors makes it difficult to identify trackable variants for a single tumor type, let alone several. Even the largest static panels may detect only a few mutations from a patient’s primary tumor, if any at all.²⁸⁻³⁰

- **Specificity is impacted by biological noise from germline and CHIP mutations.**
Without the genomic information for each primary tumor, tumor-naive assays are unable to filter out background biological noise from CHIP or to avoid tracking driver mutations that may be subjected to selection pressure from treatment.

Detecting MRD: key requirements for a clinical-grade ctDNA assay

A ctDNA assay that can accurately and reliably detect MRD to the performance level that is acceptable for clinical use must have the requirements that are highlighted in **Table 1**. Each requirement influences the expected assay performance and result interpretation, which has implications on clinical decision-making and patient care. In the next section, the available clinical evidence for tumor-informed and tumor-naive methods will be reviewed.

Table 1. Key requirements for a ctDNA assay suitable for MRD detection

| MRD assay requirements | Why it matters |
|---|---|
| The evidence reflects the intended use population | The assay’s performance should be supported with data studied in the specific patient population of interest. Incorporating additional populations will confound results. For example, when evaluating assay performance for early-stage colorectal cancer, including metastatic patients in the analysis may lead to increased sensitivity because of higher allele fraction and more easily detectable ctDNA in metastatic patients. ¹ |
| The data show post-surgical MRD performance | Data showing assay performance in the post-operative setting are needed to help support informed adjuvant treatment decisions. |
| Results are based on longitudinal performance | The assay should demonstrate sufficient clinical evidence with serial monitoring to correlate positive and negative ctDNA results with outcomes (e.g., lead time, risk of relapse with multiple negative results, etc.). |
| ctDNA levels are quantified | The ability to measure and report levels of ctDNA molecules detected in the plasma sample at each time point is a critical feature for longitudinal monitoring. |
| Performance is backed by breadth of clinical evidence | Performance of the MRD assay should be consistent across multiple tumor types and stages of cancer and should be backed by a body of clinical data. |

Clinical performance of two MRD assays in early-stage CRC

1. The evidence reflects the intended use population

Mixed patient cohorts can confound performance analysis (e.g., allele fraction of ctDNA/cfDNA is approximately 10% in stage IV patients but less than 1% in early-stage patients).¹

When choosing between different MRD assays, it is important to examine the clinical data generated in the intended use patient population. In the scenario of applying MRD testing for stage II or III colorectal cancer (CRC), sensitivity of the assay is impacted by the amount of ctDNA shed into the bloodstream, which is expected to be exceedingly low in early-stage solid tumors. MRD clinical performance in early-stage CRC should be evaluated based on data from patients without metastatic disease.

A recent study evaluating the performance of a tumor-naïve assay in CRC included 70 CRC patients, with 71% of patients in stage II or III and 19% of the patients in stage IV.¹⁹ Because the published data were not stratified by stage II/III, there is an unknown contribution of MRD detection from the stage IV patients, thus confounding performance analysis because the allele fraction of ctDNA is higher in metastatic patients.¹⁹ In contrast, Signatera was clinically validated in a more homogenous patient population. In a sample set of more than 190 CRC patients, the majority (96%) were in stages II or III (**Table 2**).^{4,7} Therefore, the data from these studies on Signatera, the tumor-informed assay, are more reflective of real-world clinical performance in stage II and III CRC patients.

Table 2. Comparison of tumor-informed assays and tumor-naïve assays for patients with early-stage CRC

| | Signatera (tumor-informed assay) ^{4,7} | Tumor-naïve assay ¹⁹ |
|-------------------------------|---|---|
| Number of CRC patients | 193 | 70 |
| Stages of CRC patients | 4% stage I; 96% stage II and III | 10% stage I; 71% stage II and III; 19% stage IV |

2. The data show post-surgical MRD performance

Assay performance will differ depending on the sampling time point (e.g., 30 days after surgery versus post-adjuvant chemotherapy).

MRD detection for early-stage disease is often used to evaluate the need for adjuvant chemotherapy (ACT) and to avoid potentially unnecessary treatment.³¹ To enable risk stratification in this setting, data on assay performance at the post-surgical MRD time point (i.e., MRD status 30 days after surgery but before chemotherapy) are required to assess the expected performance. The hazard ratio (HR) of relapse-free survival between patients with positive or negative Signatera MRD status ranges from 7.2 to 14.0 at the post-surgical time point.^{4,7,8} In contrast, data for post-surgical MRD status have not been published for the tumor-naïve assay, making it impossible to know the true performance at this critical clinical decision-point (**Table 3**). The only data to date from a tumor-naïve assay are from a blended cohort with patients across different time points.¹⁹

Positive predictive value (PPV) and negative predictive value (NPV) at each sampling time point are also key metrics when counseling patients on how to interpret positive and negative ctDNA results and what it means for their risk of residual disease and recurrence. At the post-surgical MRD time point in early-stage CRC patients, Signatera has a PPV of 97%, which means that more than 97% of patients with a positive result will relapse without additional treatment.⁴ The NPV at the same time point is 88%, which means that fewer than 12% of patients will relapse with a negative Signatera result.⁴ In contrast, data for the post-surgical MRD time point have not been validated for the tumor-naïve assay, making it impossible to know the true performance at this critical clinical decision-point (**Table 3**).

Table 3. Comparison of hazard ratios and negative predictive values of tumor-informed and tumor-naïve assays in early-stage CRC

| | Signatera (tumor-informed assay) ^{4,7,8} | Tumor-naïve assay ¹⁹ |
|--|---|---------------------------------|
| Hazard ratios of ctDNA (positive vs negative) | | |
| Post-surgery (30 day single test) | 7.2-14.0* | Not Validated |
| Post-ACT (single test) | 17.5 | 9.8-11.2** |
| Serial testing | 43.5-47.5 | 11.4 |
| Negative predictive value (NPV) | | |
| Post-surgery (30 day single test) | 88% (74/84) | Not Validated |
| Post-ACT (single test) | 86% (44/51) | 76% (37/49)** |
| Serial testing | 97% (58/60) | 82% (41/50) |

*Three in ten post-surgical positive patients cleared ctDNA with adjuvant chemotherapy and did not relapse.

**Includes patients with only post-surgery time points

3. Results are based on longitudinal performance

Treatment decisions (escalation and de-escalation) require confidence that positive and negative results are true and reliable over multiple time points.

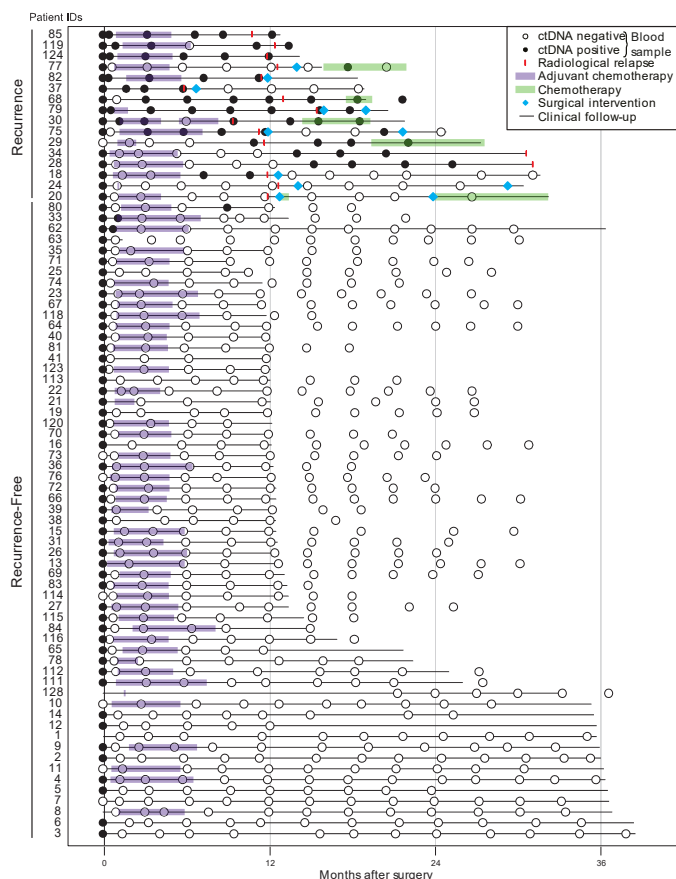
An MRD assay suitable for response and recurrence monitoring needs to show that both positive and negative results are true and remain reliable over time. To establish PPVs and NPVs, serial blood samples must be analyzed for all patients in the intended use population, including those who are non-relapsing. Serial sampling data are also important for demonstrating lead time from first MRD detection or molecular recurrence to radiographic recurrence. A test with a higher sensitivity is expected to have a longer lead time than other MRD assays and could potentially detect recurrence at the molecular level, when the disease burden is lower and curative. Based on several peer-reviewed studies, serial testing with

Signatera showed a relapse sensitivity of 92% (range: 88%–100%), demonstrating an exceptionally sensitive detection of ctDNA **(Table 4)**.³⁻⁶ False positive and false negative rates were low.³⁻⁶ In patients with early-stage CRC, Signatera detected relapse with an average lead time of 8.7 months relative to radiographic imaging.⁴ A key piece of performance data by Signatera is in the multiple time points analyzed per patient during longitudinal surveillance analysis, which clearly demonstrated the specificity and NPV of serial negative results in non-recurring patients **(Figure 2)**.⁴ With serial Signatera testing, the HR for relapse-free survival between the Signatera positive and Signatera negative patients is 43.5–47.5, and the NPV is 97% **(Table 3)**.^{4,7} The predictive power of Signatera improves with serial testing during surveillance—an important performance characteristic for an MRD test.^{4,7} Longitudinal data from a tumor-naïve assay fails to show improvement with serial testing. The HR for relapse-free survival with a tumor-naïve approach does not markedly improve (HR 11.2 at landmark vs 11.4 with serial timepoints). This information determines whether negative results from a tumor-naïve assay would hold true over time in patients initially identified as MRD negative.

Table 4. Signatera performance in the adjuvant setting across multiple tumor types

| Cancer types in the adjuvant setting | Unique patients | Plasma samples | Key findings |
|--------------------------------------|-----------------------------|----------------|--|
| NSCLC ³ | 96 Patients 14 relapses | 210 | 93% sensitivity to relapse Average lead time 4.0 months |
| Bladder ⁵ | 68 Patients 16 relapses | 651 | 100% sensitivity to relapse Average lead time 2.8 months |
| Colorectal ⁴ | 130 Patients 24 relapses | 795 | 88% sensitivity to relapse Average lead time 8.7 months |
| Breast ⁶ | 49 Patients 18 relapses | 208 | 89% sensitivity to relapse Average lead time 9.5 months |
| TOTAL | 343 Patients 72 relapses | 1864 | Sensitivity overall 92% Specificity overall 99.7-99.8% per sample |

Figure 2. Multiple longitudinal ctDNA analyses are required in relapsing and non-relapsing patients to assess assay performance for MRD



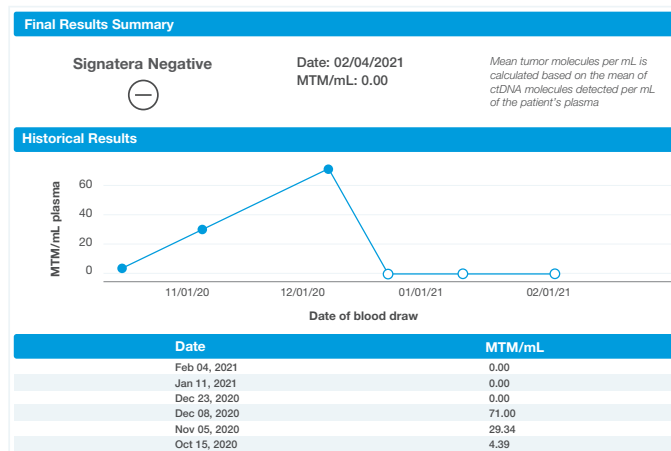
4. ctDNA levels are quantified

Correlation of ctDNA dynamics to tumor burden leads to greater accuracy in treatment response monitoring and recurrence surveillance.

Monitoring tumor response and changes in disease burden during the course of treatment or surveillance requires not only reporting the presence or absence of ctDNA, but also comparing measured ctDNA quantities over time. Tumor-naïve approaches may have difficulty with reliably reporting a quantitative measurement for MRD that combines genomic (ctDNA levels) and epigenomic signatures (e.g., methylation). In contrast, Signatera reports longitudinal ctDNA detected over time, expressed in mean tumor

molecules per mL (MTM/mL) of plasma rather than VAF (**Figure 3**). This quantitative readout takes into account for changes in background cfDNA (e.g., inflammation or surgery-related trauma), resulting in a more accurate measure of molecular disease burden. In a recent analysis of 1989 patients across multiple cancers and settings, although VAF and MTM were largely correlated ($R^2 = 0.92$), 8.8% of cases displayed discordant ctDNA levels with VAF misrepresenting the patient's disease burden.³²

Figure 3. Tumor-informed longitudinal monitoring with ctDNA reported as MTM/mL



5. Performance is backed by breadth of clinical evidence

Data from a large number of patients and blood samples are necessary for assessing test reproducibility and utility as a pan-cancer solution.

Although tumor-naïve tests offer an alternative approach for MRD detection, when they are compared to tumor-informed approaches across a number of key assay attributes, they lack in performance and breadth of data. Signatera is a personalized, tumor-informed ctDNA test that has emerged as the ideal assay for MRD assessment and treatment response monitoring. With published or presented clinical data across multiple tumor types and representing more than 2,000 patients and 6,000 plasma time points, Signatera has consistently demonstrated high sensitivity and specificity (**Figure 1, Table 5**).³⁻²⁰ While commercially available data on tumor-naïve tests reflect less than 150 patients and less than 400 time points, the body of data for tumor-informed Signatera is large, providing confidence in the expected assay performance across use cases.^{19,20}

Table 5. Data from more than 2,000 Signatera patients have been published or presented

| Author, Year | Journal/Congress | Tumor type | Patients | Plasma samples |
|--------------------------|---------------------------------|-----------------------------------|---------------------------|-------------------------|
| Abbosh et al., 2017 | <i>Nature</i> | Lung | 100 | 199 |
| Correa et al., 2019 | <i>ESMO</i> | RCC | 45 | 81 |
| Coombes et al., 2019 | <i>Clinical Cancer Research</i> | Breast | 49 | 215 |
| Reinert et al., 2019 | <i>JAMA Oncol.</i> | CRC | 125 | 795 |
| Christensen et al., 2019 | <i>J Clin Onc.</i> | Urothelial bladder carcinoma | 68 | 656 |
| Magbanua et al., 2020 | AACR | Breast, neoadjuvant | 84 | 291 |
| Cohen et al., 2020 | ESMO GI | CRC, oligo | 93* | 103 |
| Kasi et al., 2020 | ASCO | CRC, early and advanced | 535 | 715 |
| Loupakis et al., 2020 | ESMO | CRC, oligo | 113 | 192 |
| Tarazona et al., 2020 | ASCO | CRC | 193** | 1052 |
| Ococks et al., 2020 | ESMO | Esophageal adenocarcinoma | 20 | 52 |
| Hsu et al., 2017 | ASCO | HCC, advanced | 48 | 140 |
| Bratman et al., 2020 | <i>Nature</i> | IO (TNBC, melanoma, H&N, ovarian) | 94 | 316 |
| Powles et al., 2020 | ESMO IO | Urothelial bladder carcinoma | 581 | 1076 |
| Henriksen et al., 2021 | ASCO GI | CRC | 260*** | 1503 |
| Anandappa et al., 2021 | ASCO GI | CRC | 122 | 244 |
| | | Total | >2,000 patients | >6,000 plasma |

*Subset analysis of patients from Kasi et al., ASCO poster 2020

**Tarazona et al: total cohort size 193 (125 derived from Reinert cohort and 68 were unique cases)

***Henriksen et al: total cohort size 260 (125 derived from Reinert cohort and 135 were unique cases)

Conclusions

Molecular residual disease (MRD) testing is poised to revolutionize the management of patients with solid tumors. As this exciting field gains momentum, especially in early-stage CRC detection, it is important to consider test performance of the available ctDNA assays across a number of variables. Only by choosing a well-validated assay that has demonstrated the analytical and clinical rigor can we ensure that MRD results are reproducible, accurate, clinically meaningful, and useful in informing clinical decisions. This review showed that tumor-naïve approaches lack the data (performance and sample size) to appropriately characterize its expected clinical performance in the early-stage setting. Where data exist, Signatera performance across key assay requirements surpasses the tumor-naïve approaches; however, direct comparisons are challenging. Signatera is the only commercial ctDNA assay available today for MRD detection that has performance data across all key intended uses of MRD as well as consistent performance in multiple studies.

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The tests described have been developed and their performance characteristics determined by the CLIA-certified laboratory performing the test. The tests have not been cleared or approved by the US Food and Drug Administration (FDA). Although FDA is exercising enforcement discretion of premarket review and other regulations for laboratory-developed tests in the US, certification of the laboratory is required under CLIA to ensure the quality and validity of the tests. CAP accredited, ISO 13485 certified, and CLIA certified.
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